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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/729,802

12/05/2003

Bryan Julien

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EXAMINER

ROBINSON, HOPE A

ART UNIT

PAPER NUMBER

1656

DATE MAILED: 06/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/729,802

Applicant(s)

JULIEN ET AL.

Examiner

Hope A. Robinson

Art Unit

1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 January 2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) 13-19 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12 and 20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 05 December 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 5/20/04.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: Notice to Comply.

DETAILED ACTION

Application Status

1. Applicant's election without traverse of Group I (claims 1-10 and 20) on January 31, 2006 is acknowledged.
2. Claims 1-20 are pending. Claims 1-12 and 20 are under examination. Claims 11-12 as amended have been rejoined with Group I, thus the restriction requirement is withdrawn in part. Claims 13-19 are withdrawn from further consideration pursuant to 37 CFR 1.12(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.
3. The Amendment May 16, 2006 has been received and entered.

Specification

4. The specification is objected to because of the following informalities:

The specification is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 12 for example. It is suggested that http:// is deleted.

Art Unit: 1656

The specification is objected to because the title is confusing, it is suggested that the title is amended to read, "Polynucleotides Encoding Disorazole Polyketide Polypeptides".

Correction is required.

Sequence Compliance

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicant's attention is directed to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicant is required to identify all amino acid sequences of at least 4 L-amino acids and at least 10 nucleotides by a sequence identifier, i.e., "SEQ ID NO:". The specification discloses sequences that have not been identified by a sequence identifier, see for example, pages 32 and 34. The specification identifies an amino acid sequence, however, the sequence identifier is missing. If these sequences have not been disclosed in the computer readable form of the sequence listing and the paper copy thereof, applicant must provide a computer readable form of the "Sequence Listing" including these sequences, a paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and computer readable form copies are the same and, where applicable,

Art Unit: 1656

include no new matter as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See the attached Notice to Comply with the sequence rules.

Drawing

6. The drawings filed on December 5, 2003 have been accepted by the examiner.

Claim Objection

7. Claim 12 is objected to because of the following informalities:

For precision and clarity of the claim language it is suggested that claim 12 is amended to read, "A recombinant host cell", see for example claim 9.

Correction is required.

Information Disclosure Statement

8. The Information Disclosure Statement filed on May 20, 2004 has been received and entered. The references cited on the PTO-1449 Form have been considered by the examiner and a copy is attached to the instant Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is

Art Unit: 1656

most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-12 and 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to an isolated recombinant polynucleotide that comprises a nucleotide sequence encoding a disorazole polyketide synthase (PKS) protein or a fragment comprising at least one domain of said PKS. In addition, the claims are directed to the polynucleotide hybridizing under stringent conditions to a polynucleotide of SEQ ID NO:1 or its complement. Further, the claims are directed to a recombinant DNA molecule comprising a sequence of at least about 200 base pairs with a sequence identical or substantially identical to a protein-encoding region of SEQ ID NO:1. The claims encompass a genus of nucleotide and protein fragments not adequately described. Therefore, the skilled artisan cannot envision the detailed chemical structure of the genus recited in the claim, thus the claimed invention lacks adequate written description. The specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus.

A representative number of species means that the species, which are adequately described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a

Art Unit: 1656

representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. For claims drawn to a genus, MPEP 2163 states that "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In addition, MPEP 2163 states, "[t]he claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art". In this case the claims recites a polynucleotide encoding a PKS protein or fragment thereof which encompasses a genus of protein fragments; the

Art Unit: 1656

claims recite a polynucleotide that hybridizes under stringent conditions, which encompasses a genus of polynucleotide and the claims do not set forth the specific hybridization conditions and the claims recite at least about 200 base pairs and there is no guidance as to what region of the sequence is conserved or whether the sequence is a contiguous run of nucleotides, thus encompasses a genus of fragments. Given the lack of description of a representative number of species in the genus claimed, the specification fails to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

Further, *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993).

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

10 Claims 1-12 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotide set forth in SEQ ID NO: 1 and the protein encoded, does not reasonably provide enablement for the genus of nucleic acids that are encompassed in the claims and the genus of nucleotides that could hybridize to the claimed sequence, any nucleic acid fragment that is at least about 200 base pairs or any protein fragments thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)). The factors most relevant to the instant invention are discussed below.

Undue experimentation would be required to make the entire scope of the claimed invention. Claim 1 for example, is directed to "an isolated recombinant polynucleotide that comprises a nucleotide sequence encoding a disorazole polyketide synthase protein or a fragment comprising at least one domain of said PKS". Note that the claim does not provide a structure for claimed polynucleotide or the encoding protein or protein fragments. Thus, no correlation is made between structure and function and the claim is directed to a genus of protein fragments. It is noted that claim 2 recites SEQ ID NO:1, however, the claim is directed to a genus of polynucleotide that hybridizes to the claimed structure, which may not encode the same protein. In addition, the claims are directed to a polynucleotide encoding a chimeric protein, and no structure is provided for the claimed DNA or the chimeric protein. Further, the claims are directed to a fragment of the DNA and no guidance is provided as to which "at least about 200 base pairs" or whether or not said sequence is contiguous or what is substantially identical to said sequence. The claims are overly broad and include any nucleic acid that hybridizes to the claimed SEQ ID NO:1. Thus, the instant specification is not commensurate in scope with the claims.

The specification fails to provide guidance with respect to other members of the genus encompassed in the claims. The instant specification does not demonstrate or provide guidance as to what the structure of the protein will be once modified or if said protein will be functional or exhibit the same properties or characteristics as the native protein. Additionally, there is no data provided demonstrative of a particular portion of the structure that must be conserved. Therefore, the claims encompass

Art Unit: 1656

variants/fragments that may not have any biological activity. Due to the large quantity of experimentation necessary to generate the infinite number of variants/fragments recited in the claims and possibly screen same for activity and the lack of guidance/direction provided in the instant specification, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity

Art Unit: 1656

and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, *Biochemistry*, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments/variants encompassed in the claims would retain the recited function.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. Seffernick et al. (*J. Bacteriology*, vol. 183, pages 2405-2410, 2001) disclose two polypeptides having 98% sequence identity and 99% sequence identity, differing at only 9 out of 475 amino acids (page 2407, right column, middle and page 2408, Fig. 3). The polypeptides of Seffernick et al. are identical along relatively long stretches of their respective sequences (page 2408, Fig. 3), however, these polypeptides exhibit distinct functions. The modifications exemplified in the Seffernick et al. reference is small compared to those contemplated and encompassed by the claimed invention.

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. Furthermore, while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

The working examples provided do not rectify the missing information in the instant specification pertaining to the claimed variant. The nature and properties of this claim is difficult to ascertain from the examples provided as one of skill in the art would have to engage in undue experimentation to construct the variants of the claimed invention and examine the same for function.

The specification does not provide support for the broad scope of the claims, which encompasses a large variable genus of the encoding nucleic acid and polypeptide fragments. The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher*,

427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test fragments of the claimed invention would constitute undue experimentation. Making and testing the infinite number of possible fragments to find one that functions as described is undue experimentation. In addition, Guo et al. (PNAS, vol. 101, no.25, pages 9205-9210, 2004) disclose that a third of single amino acid changes would completely inactivate the average protein and the more substitutions made the more probability that the protein will be inactivated. Thus, this gives the sense of what one of skill in the art can expect when a claim embraces fragments with 10, 20, 30, 40 or more amino acid changes and how many mutants one of skill in the art can test in such an endeavor. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter, which applicant (s) regard as their invention.

Claim 2 is indefinite for the recitation of "polynucleotide that hybridizes under stringent conditions" because a sequence that hybridizes to SEQ ID NO:1 may not encode the claimed protein and the claim does not set forth what conditions are viewed as "stringent", since the art recognizes that these conditions can vary.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1 and 4-12 are rejected under 35 U.S.C. 102(e) as being anticipated by Julien et al.(U.S. Patent No. 6,410,301, November 1998, cited on IDS). The applied

reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Julien et al. disclose a nucleic acid encoding a PKS of *Sorangium cellulosum* and the utilization of the *Myxococcus xanthus* host to express said products (see claims 1-6 and columns 1-2 and 7-8 of the patent). Julien et al. disclose a vector and recombinant methods for producing polyketides in recombinant host cells (column 1). Julien et al. discloses a loading module and module one (column 2). In addition, the claimed chimeric protein is anticipated because Julien et al. teach fusion proteins with said PKS protein (see paragraph 114 of the patent). Therefore, the limitations of the claims are met by the reference.

Conclusion

13. No claims are allowable.

Art Unit: 1656

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr, can be reached at (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS *HR*

Patent Examiner *5/29/06*

**HOPE ROBINSON
PATENT EXAMINER**

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☒ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☐ 7. Other:

8. Applicant Must Provide:

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g).

For questions regarding compliance to these requirements, please contact:

- For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
- For CRF Submission Help, call (703) 308-4212
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